FATTY ACID COMPOSITION

FIELD OF INVENTION

This invention relates to fatty acid compositions.

GENERAL BACKGROUND

Cyclosporin is an important new drug developed to produce suppression of the immune system in patients receiving organ transplants, such as kidneys, hearts and livers. It is now apparent that it may have much wider uses in conditions such as psoriasis, rheumatoid arthritis, and early diabetes. It is probable but not yet certain that its effectiveness is in those conditions in which the disease process is related to abnormal functioning of part of the immune system.

Cyclosporin is an unusual cyclic peptide containing 11 amino acids. One of these is a nine carbon, olefinically unsaturated compound. Modified cyclosporins also have biological activity, but the olefinic amino acid appears important in this activity. Cyclosporin and its biologically active analogues (the cyclosporin-like compounds) all bind to a family of proteins known as cyclophilins which are found in the thymus gland, lymphocytes and other tissues. Biological activity of the cyclosporins and related compounds appears to be dependent on their ability to bind specifically to cyclophilins.

Unfortunately cyclosporin has a number of side effects, one of which is of particular importance and restricts use of the drug in disease states of only mild to moderate severity. This is that cyclosporin produces impairment of renal function. Although the mechanism of this renal damage is not yet certain, it appears that constriction of blood vessels, so reducing blood flow to the kidney, plays an important part. The mechanism of this vasoconstrictor action is also uncertain but is believed to involve increased production of thromboxane A2, a highly active vasoconstrictor derived from arachidonic acid.

It has been proposed that the renal side effects of cyclosporin may be alleviated by administering the drug in combination with metabolites of alpha-linolenic acid, namely eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) which are found in some abundance in fish oils. In animals there is experimental evidence that the treatment can lower the level of thromboxane A2 (TXA2 measured as its metabolite, thromboxane B2) in the kidney, and so reduce vasoconstriction and renal damage.

ESSENTIAL FATTY ACIDS RELATIONSHIPS AND DISCUSSION

There are two series of essential fatty acids (EFAs) which are not inter-convertible in the mammalian body but are related as shown in the following outline of essential fatty acid metabolism:

TABLE 1

n-6	n-3
18:2 delta-9,12 (linoleic acid)	18:3 delta-9,12,15 (alpha-linolenic acid)
	delta-6 desaturase ↓
18:3 delta-6,9,12 (gamma-linolenic acid)	18:4 delta-6,9,12,15

TABLE 1-continued

n-6	n-3
	elongation ↓
20:3 delta-8,11,14 (dihomo-gamma-linolenic acid)	20:4 delta-8,11,14,17
	delta-5 desaturase ↓
20:4 delta-5,8,11,14 (arachidonic acid)	20:5 delta-5,8,11,14,17
	elongation ↓
22:4 delta-7,10,13,16 (adrenic acid)	22:5 delta-7,10,13,16,19
	delta-4 desaturase ↓
22:5 delta-4,7,10,13,16	22:6 delta-4,7,10,13,16,19

The present invention depends on newly appreciated relationships of cyclosporins with essential fatty acids. As noted above, it has been proposed to ameliorate the adverse effects of cyclosporins by the countervaling effect of the fatty acids found in fish oils on TXA2 levels. However, the fatty acids found in fish oils not only reduce the amount of potentially harmful vasconstrictive thromboxane A2 formed from arachidonic acid, they also reduce the production of vasodilator metabolites such as prostaglandin E1 (PGE1) from DGLA and prostacyclin and PGE2 from arachidonic acid. The fish oil fatty acids, are therefore not the best agents to use in conjunction with cyclosporin, at least when employed alone. DGLA however, and unlike arachidonic acid, produces metabolites which are vasodilator or biologically inert in this regard, and therefore consistently has vasodilator actions. Both DGLA and arachidonic acid are found in some abundance in renal tissue. The vasodilator metabolites of both DGLA and arachidonic acid are believed to be important in the maintenance of normal renal blood flow. Since DGLA has no vasoconstrictor metabolites, it is best to employ an agent which raises levels of DGLA in the kidneys.

While DGLA can be formed from dietary linoleic acid by the pathway shown, the first step in the conversion is extremely slow in humans and in fact rate limiting. Administration of dietary linoleic acid has not been shown to be successful in raising human GLA concentrations: in contrast, by-passing the rate-limiting step by giving GLA, does raise human DGLA levels. In addition to being inherently slow, the formation of GLA is inhibited by a wide variety of factors, including ageing, atopic disorders, diabetes, catecholamines, alcohol, cholesterol, and zinc deficiency.

Administration of GLA or DGLA is an efficient way of raising the concentrations of DGLA in humans. Some of the DGLA is converted to arachidonic acid,